# Neuroendocrine carcinoma of the cervix: Review of a series of cases and correlation with outcome

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NEUROENDOCRINE CARCINOMA OF THE CERVIX: REVIEW OF A SERIES OF CASES AND CORRELATION WITH OUTCOME

ABSTRACT

Introduction: Neuroendocrine carcinoma (NEC) of the cervix is associated with a poor prognosis despite multimodal treatment. The correct diagnosis of this tumour type is imperative to provide clinicians and patients with prognostic information and ensure that appropriate treatment is provided.

Methods: A clinicopathological study was undertaken on all cervical tumours registered as NEC with the West Midlands Cancer Intelligence Unit between 01/01/1998-31/12/2009. Of the 45 cases diagnosed during the study period, the tumour samples of 41 cases were traced, anonymised and then independently reviewed by two gynaecological pathologists.

Results: The review confirmed 31/41 (78%) cases to be NEC, which overall, represented 1.3% of all the cervical cancers registered in the West Midlands over the period of the study. In the correct histological context, synaptophysin was the most sensitive and specific positive immunohistochemical marker of NEC differentiation. The cases that on review were confirmed as NEC had a significantly worse outcome than the non-NEC cases: median survival for NEC cases was 33.3 months versus 315.0 months for the non-NEC cases, p=0.013.

Conclusions: Histological review of a series of NECs has shown significantly reduced survival in those patients with confirmed NEC in comparison to those patients where a diagnosis of NEC was not confirmed. We propose morphological and immunohistochemical criteria for the diagnosis of cervical NEC; and discourage
unqualified use of the term ‘small cell carcinoma’ as this does not accurately convey
the diagnosis of SCNEC. We urge pathologists to use the 2014 WHO classification
when reporting these tumours.
INTRODUCTION

Neuroendocrine carcinomas (NEC) of the uterine cervix are uncommon, yet clinically aggressive tumours, and account for 0.5% to 1% all cervical carcinomas\(^1\). There appears to be an increasing incidence of these tumours, which is likely to be a reflection of increased recognition and diagnostic accuracy\(^2\). The diagnosis of NEC is based on accurate histopathological and immunohistochemical identification of neuroendocrine features. The nomenclature of these tumours has changed several times over the years leading to inconsistent use of terminology by pathologists. The first approach at unifying terminology was in 1996 when the College of American Pathologists and the National Cancer Institute sponsored a workshop designed to “reduce the number of terms used to describe these lesions”. They suggested dividing endocrine tumors of the cervix into four categories: typical (classical) carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma, and small (oat) cell carcinoma\(^3\). The last term is often confused with the small cell squamous carcinoma of the uterine cervix. The current WHO classification of cervical carcinomas\(^4\) is similar to that used for gastro-entero-pancreatic neuroendocrine carcinomas. According to the recent World Health Organization (WHO) classification, gastro-entero-pancreatic neuroendocrine carcinomas are classified as grade 1 neuroendocrine tumors (G1 NETs), grade 2 neuroendocrine tumors (G2 NETs), and grade 3 neuroendocrine carcinoma, large cell (G3 NEC-LC) or small cell (G3 NEC-SC) subtype\(^5\).

We present a large case series of neuroendocrine carcinomas of the cervix with an emphasis on the accurate diagnostic features of these tumours.
MATERIALS AND METHODS

Between 1998 – 2009, 45 cases of NEC were registered with the West Midlands Cancer Intelligence Unit, a population based cancer registry mandated to collect information on all cases of cancer within the specified geography. Ethical approval was granted for a clinicopathological study of these tumours (10/H1206/24) and the research registered under the responsibility of the Birmingham Women’s NHS Trust research governance arrangements. All available tissue blocks, histological sections and pathology reports were requested from the diagnosing hospitals and anonymised by designated staff at the Cervical Screening Quality Assurance team and the Cancer Information Manager at the West Midlands Cancer Intelligence Unit (WMCIU) (subsequently becoming part of Public Health England). All anonymised slides were reviewed by one of two specialist gynaecological pathologists (RG and LH), and the cases in which the diagnosis of NEC was changed, as well as a random 10% of the cases, were reviewed by both pathologists.

The morphological diagnosis of small cell neuroendocrine carcinoma (SCNEC) was made when the tumour showed most of the following cytonuclear features: nuclear hyperchromasia, high nucleocytoplasmic ratio, scanty cytoplasm, nuclear moulding with or without streaming artifact, necrosis, apoptosis, brisk mitotic and apoptotic activity. Large cell neuroendocrine carcinomas (LCNEC) were diagnosed using the same criteria as for pulmonary LCNEC. These criteria included (1) cells of large size, polygonal shape and low nucleocytoplasmic ratio, (2) nuclei with coarse chromatin and prominent nucleoli and (3) mitotic activity in excess of 10 mitotic figures per 10 high-power fields (X40 magnification). An admixed squamous component was diagnosed in the presence of keratinisation or intercellular bridges. Admixed
adenocarcinoma was diagnosed when glandular structures or mucin-containing cells were present. The presence of cervical intra-epithelial neoplasia (CIN) and cervical glandular intra-epithelial neoplasia (CGIN) were recorded. The presence or absence of vascular invasion and perineural invasion was noted.

All tumours were assessed for immunohistochemical expression of Ki67, chromogranin, synaptophysin, CD56, p63, TTF-1, p16 and CAM5.2. The majority of cases had some, if not all, of the immunohistochemistry performed at the time of the original diagnosis and additional immunohistochemistry was requested where necessary, for completion of the panel. For all antibodies except Ki67, cases were scored as 0 (negative), 1 (1 – 25% of cells positive), 2 (26 – 50% of cells positive) and 3 (>50% of cells positive). Ki67 was scored as 0 (negative), 1 (1 – 25% of cells positive), 2 (26 – 50% of cells positive), 3 (51 – 75% of cells positive) and 4 (>75% of cells positive). For CAM5.2 immunohistochemistry, the pattern of staining was recorded as diffuse when cytoplasmic and membranous staining were present, and as dot-like when punctate, paranuclear cytoplasmic staining was seen.

RESULTS

The diagnostic material was available for 41 of the 45 cases and in all but one case of small cell neuroendocrine carcinoma (SCNEC) there was sufficient material to complete the immunohistochemical panel. The specimens available for review were mostly cervical biopsies, 34 cases, however cervical loop excision biopsies (4 cases) and hysterectomy specimens (3 cases) were also included.
Of the 41 cases were reviewed, the diagnosis of NEC was confirmed on review in 31 cases: 23 cases of SCNEC, 8 cases of LCNEC (Figure 1) and 10 cases of non-NEC tumours (Table 1). Admixed non-NEC components were seen in 12 of the NEC tumours (Table 2). CIN was present in the 3 cases of squamous carcinoma with LCNEC and high-grade CGIN was seen in 2 SCNEC (Figure 2) and 1 LCNEC, both cases had associated adenocarcinomas. Lymphovascular space invasion was seen in 3/23 SCNEC (13.0%), 5/8 LCNEC (62.5%) and 2/10 non-NEC (20.0%) cases. Invasion of multiple vessels was seen in 3/8 NEC (37.5%) cases. Perineural invasion was only seen in one SCNEC and one non-NEC (squamous cell carcinoma).

Immunohistochemistry showed that irrespective of the intensity of staining, 14 of 23 SCNEC (60.8%) and 6 of 8 LCNEC (75%) were positive for chromogranin; 19 of 23 SCNEC (82.6%) and 7 of 8 LCNEC (87.5%) were positive for synaptophysin; and 15 of 23 SCNEC (65.2%) and 7 of 8 LCNEC (87.5%) were positive for CD56 (Figure 3) (Table 3). In 6 cases of NEC (5 SCNEC and 1 LCNEC) synaptophysin was the only neuroendocrine marker that was expressed. In contrast, none of the non-NEC expressed chromogranin and synaptophysin whilst one showed CD56 positivity in <25% of cells. Therefore, of the neuroendocrine markers, synaptophysin was the most sensitive and specific in identifying NEC differentiation.

p63 staining was a strong predictor of non-NEC differentiation being expressed by 6/10 (60%) non-NEC tumours (Figure 4). CAM5.2 marked 16/23 (69%) of SCNEC, 7/8 LCNEC (87.5%) and all non-NECs. Dot-like positivity was seen in 43% of SCNEC (Figure 5) and 12% of LCNEC. None of the non-NECs showed dot-positivity. TTF-1 was negative in 18 of 23 (78%) of SCNEC and did not stain any of the LCNEC or non-NECs. p16 stained all the carcinomas studied.
The original diagnosis was available to the review pathologists only after completion of the review. The terminology used for the original diagnoses was varied. Of the 23 cases with a review diagnosis of SCNEC, 10 were originally diagnosed as SCNEC, 3 as NEC not otherwise specified (NOS), 5 as small cell carcinoma NOS, 2 as poorly-differentiated carcinomas, 2 as LCNEC and the rest as malignant neoplasm NOS, peripheral neuroectodermal tumour (PNET) and poorly-differentiated carcinoma. Of the 8 cases with a review diagnosis of LCNEC, 1 had a primary diagnosis of LCNEC, 2 were diagnosed as SCNEC, 2 cases as poorly-differentiated carcinoma, 1 as undifferentiated carcinoma with NE features, 1 as small cell carcinoma with limited neuroendocrine features and 1 NEC NOS. Histological review did not confirm the diagnosis in 10 cases. Five cases were diagnosed as undifferentiated or poorly differentiated carcinomas on review, 2 of the 5 were squamous cell carcinomas with very scanty foci of keratinisation, 2 were adenosquamous and adenocarcinomas where glandular differentiation was scanty and 1 was determined to be an undifferentiated carcinoma even after review. Of the remaining 5 cases, 2 were small cell carcinomas that were diagnosed as squamous cell carcinoma on review, 1 was a NEC NOS and reviewed as squamous cell carcinoma, 1 was an adenosquamous carcinoma with NE differentiation reviewed as an adenosquamous carcinoma and 1 was an adenocarcinoma with NE differentiation reviewed as an adenocarcinoma. In 7 of the 10 cases with altered diagnoses, the original suggestion or diagnosis of neuroendocrine carcinoma or differentiation was based on focal expression of neuroendocrine markers, mostly NSE and synaptophysin and one case with focal (<10%) strong CD56 expression. In 2 of 10 cases with altered diagnosis, the original interpretation of focal chromogranin expression was, on review, found to be incorrect.
In 6 of 10 cases with altered diagnosis, p63 staining was positive. Of the cases that were reviewed as non-NECs, one case had high-grade CGIN and another CIN3.

The cases that were recognised as non-NEC on review had a significantly better outcome than the NEC cases. Median survival for NEC cases was 33.3 months versus 315.0 months for the non-NEC cases, log-rank 0.013 (Figure 6).

DISCUSSION

Cervical NECs are rare but highly aggressive neoplasms known for their poor prognosis\(^1,6\) and marked propensity for systemic spread\(^6\). Their management differs from that of non-NEC cervical cancers with regard to the choice of chemotherapy regimen and treatment modality scheduling. Ensuring an accurate diagnosis in such cases is vitally important since it is the basis on which all future clinical management decisions will be made as well as forecasting poor long-term survival. Accurate data for survival of patients with NEC of the cervix are difficult to obtain because of the variation in terminology that has been used for these tumours over time\(^7\) and to date publications on NECs have rarely included pathology reviews to verify the diagnosis\(^8-10\).

Our study refines the evidence available in literature by including pathology reviews. It confirms that the cases which were categorized as non-NEC on review had a significantly better survival than the confirmed NEC cases; median survival for patients with NEC cases was 33.3 months versus 315.0 months for those non-NEC cases. Before reclassifying 10 cases as non-NECs, our series of cases identified that NECs constituted 1.3% of all cervical carcinomas in the West Midlands region during
the study period, an incidence that is in keeping with the published literature\(^1\). The 94-year-old woman with a diagnosis of LCNEC is the oldest reported case of neuroendocrine carcinoma in the literature.

Neuroendocrine differentiation was suspected morphologically in the presence of a high mitotic rate, geographical necrosis and a lack of specific differentiation features such as keratinisation. This was supported by the Ki67 staining in SCNEC where >75% of cells were positive; only 9% showed less than 25% staining. Ki67 expression has not been previously assessed as a supportive diagnostic feature. Typically immunohistochemistry for three markers - synaptophysin, chromogranin and CD56 - is attempted for confirmation. In our study we found synaptophysin to be the most specific and sensitive marker of neuroendocrine differentiation. This is borne out by observations in literature where a specificity of 64 - 73% is noted\(^11\)\(^12\). The sensitivity of NSE is high, up to 81.8\(^{11}\), however its specificity is low and it suffers from poor laboratory reproducibility\(^13\)\(^14\). With the discovery of more specific antibodies, its use has declined\(^15\) and although the use of immunohistochemistry is helpful in confirmation; the diagnosis of high-grade neuroendocrine carcinoma is still based on morphology.

The rarity of these tumours contributes to their diagnostic challenge. In SCNEC cases this is likely to be due to their shared morphological similarity with NECs arising from other anatomical sites, whereas LCNEC are rarer than SCNEC and are more commonly misdiagnosed\(^16\)\(^17\). This is perhaps unsurprising when considering that historically LCNEC was recognised as a specific tumour type later than SCNEC. Most of the difficulties in this study came in separating LCNEC from adenosquamous carcinoma. The large cell size and eosinophilic cytoplasm of the tumour cells results
in an squamoid appearance. When keratinisation is not noted, a default diagnosis of poorly-differentiated squamous or adenosquamous carcinoma is usually considered. The high mitotic rate and geographic necrosis are features that should alert the pathologist to the possibility of a LCNEC. In our study we found a high incidence of vascular invasion in LCNEC. This is well documented in literature\(^{16-18}\). All of the cases of LCNEC expressed at least two of the three neuroendocrine markers. The Ki67 index, whilst not as high as SCNEC, was present in majority of cells in 66% of LCNEC.

Unlike SCNEC, p63 expression proved unhelpful as most of the adenosquamous carcinomas and the undifferentiated carcinoma, for which the LCNEC were mistaken, were also p63 negative. In the SCNEC cases however, p63 was more useful as it was noted in the majority (67%) of the non-NEC carcinomas in our study, whereas none of the SCNEC showed p63 expression. We therefore consider lack of p63 staining to be a strong pointer towards a diagnosis of neuroendocrine differentiation in the correct histomorphological context. p63 is expressed in the basal and parabasal layers of the squamous epithelium in the cervix, vagina and vulva, and is noted to be a key feature in squamous epithelial development in murine models\(^{21}\). In some studies, NEC have been noted to stain weakly for p63\(^{22,23}\). In a study of 43 neuroendocrine lung carcinomas, Travis and colleagues \(^{19}\) showed that when there was interobserver variation amongst experienced pathologists in the categorisation of lung carcinomas p63 aided the distinction and subsequent accurate classification. Studies on p40 in lung carcinomas show that this marker is more sensitive than p63 in diagnosing squamous differentiation in poorly differentiated carcinomas\(^{24,25}\), however p40 is a relatively new antibody and has not yet been studied in cervical carcinomas.
Cutaneous neuroendocrine carcinomas (Merkel cell tumours) are reported to show paranuclear dot-like staining with cytokeratins\(^{26}\). In our cohort, CAM 5.2 stained nearly 80% of NECs and 100% of non-NECs, with dot-like positivity being seen in both groups. We conclude that the dot-like pattern of staining is not specific for neuroendocrine tumours. TTF-1 is a well-known, useful marker of pulmonary adenocarcinoma and small cell carcinomas and it is also known to be positive in small cell carcinoma of the bladder\(^{27}\). In our study, TTF-1 stained 5 of 23 cases (21.7%) of SCNEC and none of the cases of LCNEC, lower than reported other studies\(^ {28}\). We conclude that TTF-1 is not a useful marker in the diagnosis of NEC of the cervix.

The terminology of cervical NEC has undergone several revisions. In 1996, a specific classification for neuroendocrine neoplasms of the cervix was proposed at a workshop convened under the auspices of the College of American Pathologists and the National Cancer Institute\(^3\). The WHO classification (2003)\(^ {29}\) then incorporated neuroendocrine tumours into the category of other epithelial tumours, and subcategorised this group of tumours into carcinoid, atypical carcinoid, small cell carcinoma and large cell neuroendocrine carcinoma, akin to the classification used for pulmonary neuroendocrine neoplasms\(^ {30,31}\). Unlike the specific designation of LCNEC, neither classification explicitly defined the ‘small cell’ carcinomas as being of neuroendocrine type. This has lead to diagnostic confusion because the term ‘small cell tumour’ of the cervix includes a range of tumours of small cell type e.g. basaloid and small cell squamous carcinomas, undifferentiated carcinoma, melanoma, rhabdomyosarcoma and lymphoma. If the non-epithelial malignancies are excluded, basaloid and small cell squamous carcinomas remain the main differential diagnoses of small cell carcinoma of neuroendocrine type. The basaloid variant of squamous cell carcinoma (SCC) is typified by small cells with round nuclei and inconspicuous
nucleoli. Not all basaloid SCCs show keratin production; and while the presence of keratinisation is useful, this cannot be used as at the sole criterion for the diagnosis of basaloid SCC. Although there is morphological overlap between basaloid SCCs and SCNEC, the two tumours are managed very differently and have differing prognoses. The accurate diagnosis of SCNEC can be even more difficult in small biopsies. The current WHO classification of cervical carcinomas is similar to that used for gastro-entero-pancreatic neuroendocrine carcinomas. This classification unifies all cervical neuroendocrine tumours and encourages the use of immunohistochemistry to confirm the diagnosis. It subdivides them into low- and high-grade and does not include poorly-defined and descriptive terminology such as cell size alone. We believe that this will encourage accurate diagnosis, an assumption that will need further review.

In summary, we propose the use of strict morphological criteria and application of selected immunohistochemical markers to allow confident identification of the vast majority of cervical tumours of this clinically significant histological subtype. When a diagnosis of a high-grade carcinoma of the cervix is entertained, an immunohistochemical panel of synaptophysin, chromogranin, CD56, p63 and Ki67 should be used to confirm neuroendocrine differentiation and the diagnosis should be conveyed unambiguously in the pathology report. The presence of lymphovascular invasion, necrosis, a high mitotic rate and expression of neuroendocrine markers are all pointers to the correct diagnosis. We urge all pathologists reporting cervical specimens familiarize themselves with the WHO 2014 classification of these tumours.
CONCLUSION

A diagnosis of neuroendocrine carcinoma impacts greatly on the clinical management and outcome of patients with cervical carcinoma. Histological review of a series of NECs has shown significantly reduced survival in those patients with confirmed NEC in comparison to those patients where a diagnosis of NEC was not confirmed. We propose morphological and immunohistochemical criteria for diagnosis of cervical NEC, and discourage unqualified use of the term ‘small cell carcinoma’ as this does not accurately convey the diagnosis of SCNEC. We urge pathologists to use the 2014 WHO classification when reporting these tumours.

ACKNOWLEDGEMENTS

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REFERENCES


Table 1. Demographics and survival of patients with small cell neuroendocrine carcinomas (SCNEC), large cell neuroendocrine carcinomas (LCNEC) and non-neuroendocrine cervical carcinomas (Non-NEC).

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<thead>
<tr>
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<th>SCNEC (n=23)</th>
<th>LCNEC (n=8)</th>
<th>Non-NEC (n=10)</th>
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<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(median and range)</td>
<td>42 (23-79)</td>
<td>55.5 (22-94)</td>
<td>44.5 (22-73)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stage I</td>
<td>3 (13%)</td>
<td>2 (25%)</td>
<td>3 (30%)</td>
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<tr>
<td>Stage II+</td>
<td>19 (83%)</td>
<td>6 (75%)</td>
<td>7 (70%)</td>
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<tr>
<td>Unknown</td>
<td>1 (4%)</td>
<td>0</td>
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<tr>
<td>Median survival (months)</td>
<td>13.2 (0.2-57.3)</td>
<td>12.2 (0.3-50.7)</td>
<td>124.3 (7.4-124.3)</td>
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Table 2. The presence of admixed non-neuroendocrine (non-NEC) components in the cohort of small cell neuroendocrine carcinomas (SCNEC) and large cell neuroendocrine carcinomas (LCNEC).

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<th>SCNEC (n=23)</th>
<th>LCNEC (n=8)</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>5 (21.7%)</td>
<td>2 (25%)</td>
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<tr>
<td>Squamous carcinoma</td>
<td>1 (4.3%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1 (4.3%)</td>
<td>0</td>
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<tr>
<td>No non-NEC components</td>
<td>16 (69.6%)</td>
<td>3 (37.5%)</td>
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Table 3. Immunohistochemistry results of small cell neuroendocrine carcinomas (SCNEC), large cell neuroendocrine carcinomas (LCNEC) and non-neuroendocrine cervical carcinomas (non-NEC). Results are not available for all SCNEC cases due to a paucity of tumour tissue in 2 cases. Figures given in brackets are percentages.

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<th>LCNEC (n=8)</th>
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<th>Non-NEC (n=10)</th>
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<tr>
<td></td>
<td>Neg</td>
<td>&lt;25%</td>
<td>25-50%</td>
<td>&gt;50%</td>
<td>Neg</td>
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<td>Chromogranin</td>
<td>8 (35)</td>
<td>4 (17)</td>
<td>3 (13)</td>
<td>7 (30)</td>
<td>2 (25)</td>
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<tr>
<td>Synaptophysin</td>
<td>3 (13)</td>
<td>5 (22)</td>
<td>2 (9)</td>
<td>12 (52)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>CD56</td>
<td>8 (35)</td>
<td>3 (13)</td>
<td>2 (9)</td>
<td>10 (43)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>p63</td>
<td>23(100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7 (88)</td>
</tr>
<tr>
<td>TTF1</td>
<td>16 (73)</td>
<td>2 (9)</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>8 (100)</td>
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<tr>
<td>p16</td>
<td>0</td>
<td>0</td>
<td>2 (9)</td>
<td>20 (91)</td>
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<tr>
<td>CAM5.2</td>
<td>6 (26)</td>
<td>3 (13)</td>
<td>4 (17)</td>
<td>10 (43)</td>
<td>0</td>
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<tr>
<td>Ki67</td>
<td>0</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>18 (86)</td>
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High power view showing a high-grade neuroendocrine carcinoma of large cell type. The cells have scanty cytoplasm and apoptotic bodies are interspersed. (X400 magnification) 1071x1016mm (33 x 26 DPI)
High-grade neuroendocrine carcinoma of small cell carcinoma admixed with high grade cervical glandular intraepithelial neoplasia (high grade CGIN). The small cells have hyperchromatic and smudged nuclei, nuclear pleomorphism and scanty cytoplasm. The glandular epithelium shows nuclear stratification and mitotic activity. (X200 magnification)
The high-grade neuroendocrine carcinoma shows strong membranous staining with CD56. (X200 magnification)
1071x1016mm (33 x 26 DPI)
Immunohistochemistry of a non-keratinising squamous carcinoma shows nuclear staining with p63. (X400 magnification)
236x164mm (144 x 144 DPI)
The high grade neuroendocrine carcinoma shows cytoplasmic staining with CAM 5.2. In many cells, the staining is paranuclear and dot-like. (X400 magnification)

685x514mm (96 x 96 DPI)
Overall survival for neuroendocrine carcinomas (NEC) n=31, and non-neuroendocrine cervical carcinomas (non-NEC) n=10, Log-rank p=0.013
185x126mm (300 x 300 DPI)